A pathway for Parkinson's Disease LRRK2 kinase to block primary cilia and Sonic hedgehog signaling in the brain.

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Public Summary:
Parkinson's disease-associated LRRK2 kinase phosphorylates multiple Rab GTPases, including Rab8A and Rab10. We show here that LRRK2 kinase interferes with primary cilia formation in cultured cells, human LRRK2 G2019S iPS cells and in the cortex of LRRK2 R1441C mice. Rab10 phosphorylation strengthens its intrinsic ability to block ciliogenesis by enhancing binding to RILPL1. Importantly, the ability of LRRK2 to interfere with ciliogenesis requires both Rab10 and RILPL1 proteins. Pathogenic LRRK2 influences the ability of cells to respond to cilia-dependent, Hedgehog signaling as monitored by Gli1 transcriptional activation. Moreover, cholinergic neurons in the striatum of LRRK2 R1441C mice show decreased ciliation, which will decrease their ability to sense Sonic hedgehog in a neuro-protective circuit that supports dopaminergic neurons. These data reveal a molecular pathway for regulating cilia function that likely contributes to Parkinson's disease-specific pathology.

Scientific Abstract:
Parkinson's disease-associated LRRK2 kinase phosphorylates multiple Rab GTPases, including Rab8A and Rab10. We show here that LRRK2 kinase interferes with primary cilia formation in cultured cells, human LRRK2 G2019S iPS cells and in the cortex of LRRK2 R1441C mice. Rab10 phosphorylation strengthens its intrinsic ability to block ciliogenesis by enhancing binding to RILPL1. Importantly, the ability of LRRK2 to interfere with ciliogenesis requires both Rab10 and RILPL1 proteins. Pathogenic LRRK2 influences the ability of cells to respond to cilia-dependent, Hedgehog signaling as monitored by Gli1 transcriptional activation. Moreover, cholinergic neurons in the striatum of LRRK2 R1441C mice show decreased ciliation, which will decrease their ability to sense Sonic hedgehog in a neuro-protective circuit that supports dopaminergic neurons. These data reveal a molecular pathway for regulating cilia function that likely contributes to Parkinson's disease-specific pathology. Editorial note: This article has been through an editorial process in which the authors decide how to respond to the issues raised during peer review. The Reviewing Editor's assessment is that all the issues have been addressed (see decision letter).